NTP NOMINATION HISTORY AND REVIEW

1,2-DIBROMO-2,4-DICYANOBUTANE

CAS No. 35691-65-7

NOMINATION HISTORY

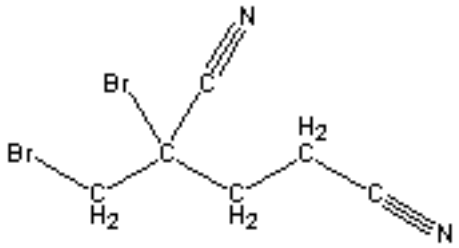
1.	Nomination Source:	NIEHS
2.	Recommendations:	- Genetic toxicity - Toxicology
3.	Rationale/Comments:	- Potential human exposure (consumer) - Lack of carcinogenicity testing
4.	Priority:	
5.	Date of Nomination:	

SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

CAS Registry Number:	35691-65-7
Chemical Abstract Services Name:	Pentanedinitrile, 2-bromo-2-(bromomethyl)- (9CI)
Synonyms:	2-Bromo-2-(bromomethyl)glutaronitrile; methyldibromoglutaronitrile; Tektamer 38
Structural Class:	Halogenated aliphatic nitrile

Structure, Molecular Formula and Molecular Weight:



$C_6H_6Br_2N_2$ Mol. wt.: 265.94

Chemical and Physical Properties

Description:	Off-white to light tan crystalline powder (CIR, 1994); mildly pungent odor (Budavari, 1989)
Melting Point:	50-53^{o}C (CIR, 1994)
Solubility:	Soluble in water (0.212 g/100 ml at 20^{o}C) (CIR, 1994); very soluble in acetone, benzene, chloroform, dimethylformamide, and ethyl acetate; soluble in diethyl ether, ethanol, and methanol (Budavari, 1989)

Technical Products and Impurities: 1,2-Dibromo-2,4-dicyanobutane (DBDC) is available as a 98.5% pure substance (for use in cosmetic products). Impurities found include: water, 1.5% (max.); bromide, 0.1% (max.); total organic impurities, 100 ppm (max.); and iron, 5 ppm (max.) (CIR, 1994)

The following products are available from Calgon Corp.: Merguard 1200, a 20% active solution of DBDC in phenoxyethanol; Merguard 1190, a 10% active solution of DBDC in dipropylene glycol; Tektamer 38AD, a 25% aqueous dispersion; Tektamer 38, a 98% powder; and Tektamer

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LV, a 25% slurry (Anon., 1982a, 1995; Weber, 1996). Euxyl K400, a synergistic mixture of DBDC and phenoxyethanol in the ratio of 1:4, is available from Calgon Corp. and Schulke & Mayr (CTFA, 1991; Ross *et al*., 1992).

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EXPOSURE INFORMATION

Production and Producers: DBDC is prepared by reacting bromine with 2-methyleneglutaronitrile at temperatures below 30°C (CIR, 1994). The U.S. patent for the synthesis of DBDC was issued to Merck & Co. in 1974 (Budavari, 1989).

DBDC is listed in the EPA's TSCA Inventory (NLM, 1996). The annual U.S. production of DBDC was estimated to be in the range of 300,000 to 400,000 pounds (Baron, 1996). No other information on annual production volume was found in the available literature. However, DBDC was listed as a chemical in commerce in the U.S. International Trade Commission (USITC) publication *Synthetic Organic Chemicals, US Production and Sales* 1984-1989, 1991-1993 (USITC, 1985, 1986, 1987, 1988, 1989, 1990, 1993, 1994a, 1994b). The reporting companies were Merck & Co., Inc. (1984-1989) and Pfister Chemical, Inc. (1991-1993). According to the USITC, separate statistics were not published to avoid disclosure of individual company operations. Although no specific production data were reported, the USITC reporting guidelines specify that each company's report of a chemical represents manufacture of a quantity $\geq$ 4,500 kg (10,000 lbs] or sales $\geq$ $10,000.

DBDC is currently produced in the U.S. by Pfister Chemical, Inc. and Calgon Corp., a subsidiary of Merck & Co. (Baron, 1996; Weber, 1996).

Use Pattern: DBDC is used as a preservative in paints, emulsions, dispersed pigments, adhesives, joint cements, metalworking fluids, cosmetics, paper, inks, waxes, and household products. DBDC protects water-based systems from a broad range of microorganisms including bacteria, fungi, yeast, and algae. As a biocide, it is effective at treatment levels generally well below 0.1% (Anon., 1982b).

The product formulation data submitted to the Food and Drug Administration (FDA) in 1994 reported that DBDC was used in 35 cosmetic formulations. Cosmetic products containing DBDC included eyeliners, eye shadow, powders, hair conditioners, hair sprays, shampoos, blushers, cleansing agents, depilatories, moisturizing preparations, indoor tanning preparations, and manicuring preparations. It is found in cosmetic formulations at concentrations ranging from 0.0075% to 0.06% for the active substance (CIR, 1994).
Reports in the literature indicate that the use of DBDC is rapidly increasing (Ross *et al*., 1992; Hausen, 1993; Weyland *et al*., 1994; Van Ginkel & Rundervoort, 1995). In 1994,

approximately 20% of all cosmetics sold in the Dutch market contained DBDC (Weyland *et al*., 1994).

Human Exposure: There is potential for occupational and consumer exposure to DBDC.

Occupational

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 17,712 workers, including 3,345 female employees were potentially exposed to DBDC in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NIOSH, 1990).

Consumer

There is the potential for consumer exposure to DBDC through its use in cosmetic and household products. Cosmetic products containing DBDC may be applied to or come in contact with skin, eyes, hair, nails, and mucous membranes. Daily or occasional use may extend over many years (Anon., 1982b; CIR, 1994).

Environmental Occurrence: DBDC is not known to occur naturally. No information was found in the available literature identifying DBDC in environmental media.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of DBDC. The American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) for this compound.

DBDC is registered with the EPA and FDA for use in products that come under the jurisdiction of these agencies. It is a pesticide, subject to registration or reregistration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The FDA has approved the use of DBDC in adhesives which may be used in products in contact with foods. It has also been approved for use in slimicides, and latex emulsions (Lederer *et al*., 1982; NLM, 1996).

The Cosmetic Ingredient Review Expert Panel of the Cosmetic, Toiletry, and Fragrance Association has approved DBDC as safe as used in rinse-off products, and safe up to 0.025% in leave-on products. The concentration of use for rinse-off products was expected to be up to 0.06% (CIR, 1994).

DBDC is restricted to a maximum authorized concentration of 0.1% in cosmetic products by the European Economic Commission and is not to be used in cosmetic sunscreen products at a concentration exceeding 0.025% (CIR, 1994).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to DBDC and cancer risk in humans were identified in the available literature. Based on human repeat insult patch testing, DBDC was found to be a non-sensitizer at concentrations between 0.0012 and 0.0396% (CIR, 1994). However, several case studies reported positive DBDC patch tests. The case studies are summarized in Table 1.

Table 1. Case reports of DBDC patch tests

Concentration	Comments	Results (Positive/Tested)	Reference
0.5% ethanol* 0.5% pet.*	cosmetics were found to have sensitized 8/24; of 11 patients further tested, 3/11 had mild reactions to 0.1% DBDC, 5/11 developed itching dermatitis after 2 wks of lotion containing 0.02%* DBDC	24/2057 dermatitis patients	Tosti *et al.*, 1991
0.2%* pet.	2 positives seen in females who had developed severe eyelid eczema after using cucumber eye gel containing 0.1%* DBDC; when these 2 further tested to 0.02%*, mild to moderate reactions were seen	2/27 - 2 patients, 25 controls	Ross *et al.*, 1992; CIR, 1994
0.04%* aq. eth.	all of the allergic patients suffered from widespread eczema	5/889 dermatitis patients	Corazza *et al.*, 1993
0.1% pet. 0.01% pet.	patient also tested positive to her cucumber eye gel and the preservative in the gel which contained DBDC	1/11 - 1 female patient, 10 controls	O'Donnell & Foulds, 1993
0.1%* pet.	patient developed acute eczema following application of an ultrasonic gel preparation; sensitization believed to be contracted non-occupationally from a cosmetic or toiletry	positive patch test in male patient	Gebhart *et al.*, 1993
0.1% pet.	female patient developed acute dermatitis with erythema and vesicles following 12 days use of a gel bath product; patch test results were negative for other components of the gel	strongly positive reaction to patch test	Pigatto *et al.*, 1991
0.03%* 0.4%*	 at 0.4%, 8 reactions interpreted as irritant	18/1033 suspected dermatitis patients 21/1033 suspected dermatitis patients	Motolese *et al.*, 1991
0.5% pet. 0.1%, 0.03% 0.01%,0.003% 0.001% al.	male patient with worsening symptoms of pruritus ani and itching on arms was sensitized to moist toilet paper	bullous reaction seen in male patient strongly positive reactions to all concentrations seen in above male patient. 25 controls had no reaction to 0.1%	DeGroot *et al.*, 1991
0.001-0.1% w/w pet.	2-3+ eczematous reactions in 1 male maintenance mechanic in a baby food processing plant who developed acute eczema related to a paste glue containing DBDC	1/31 - 1 patient, 30 controls	Mathias, 1983

0.1% pet.	12 of the 16 positive patients had intensively used moistened toilet tissues which contained a preservative formulated with DBDC	1/286, 9/281, 6/247 positive reactions in consecutive patients for first half and second half of 1993 and first half of 1994, respectively	Van Ginkel & Rundervoort, 1995

* Actual compound tested was a trade name preservative of which DBDC comprises 20%. The other component of the preservative was 2-phenoxyethanol which was found to be a weak sensitizer on its own. The percentages in the table have been adjusted to reflect the concentration of DBDC contained in the patch.

Animal Data: Unless otherwise specified, information in the following sections is from CIR (1994). Data were taken from unpublished reports submitted by the manufacturers and independent contract laboratories.

Acute/Subacute

Acute toxicity data reported for DBDC are shown below:

rat (male) oral LD_{50} = 770 mg/kg

rat (female) oral LD_{50} = 515 mg/kg

rabbit dermal LD_{50} = > 5 g/kg

rat inhalation LC_{50} = > 13.1 mg/L

A short term dermal toxicity study indicated that DBDC was a severe dermal irritant when applied to male and female rats (strain not specified) at doses up to 4 g/kg for 6 hours a day for 21 days. While no raw data were provided, moderate to severe eschar by week 2 was reported in all dosed animals; none was observed in controls. Feed consumption decreased at day 8 in high- and mid-dose males. There was no evidence of systemic toxicity. Analysis of blood samples obtained at the end of the study indicated "slight but consistent decreases" in hematocrit, hemoglobin concentrations, and red blood cell counts in the treated groups, particularly the high dose. Other tested blood levels remained within the reference range.

A 28-day dermal toxicity study indicated that 0.025% DBDC caused slight to moderate local irritation when applied to the shaved and abraded skin of male and female New Zealand rabbits. DBDC at 0.025% in formulation or 0.3% in an aqueous dilution of the trade ingredient was applied at 2 ml/kg body weight 5 days a week for 4 weeks. The test sites of animals treated with 0.025% DBDC showed moderate to severe erythema and slight to moderate edema. Slight to moderate acanthosis, mild to slight hyperkeratosis, and minimal to moderate inflammatory infiltration were noted and one animal had slight focal

necrosis and slight focal abscessation of the test site. The test sites of animals treated with 0.3% showed slight erythema, slight focal or diffuse acanthosis and minimal focal inflammatory infiltration. Two animals from each exposure group developed slight reactive submandibular lymph node hypertrophy which the researchers concluded to be an indirect response to cutaneous irritation. Differential WBC counts for females dosed with 0.025% revealed a relative neutrophilia interpreted as perhaps indicative of a mild inflammatory response to treatment. The researchers do not address the findings that the higher dosed animals exhibited less severe responses.

Ocular and Dermal Irritation/Sensitization

DBDC was a severe primary ocular irritant when instilled into the conjunctival sacs of rabbits at a dosage of 0.1 g (98% active, powder form). The irritation was significantly reduced when 0.1 ml of a 2% dilution of DBDC was instilled.

Slight to moderate erythema and edema were observed when 0.5 g of DBDC (98% active, powder form) was dermally applied to rabbit skin.

Results of 7 guinea pig dermal sensitization studies following the Ritz-Buehler method, using induction and challenge concentrations between 0.2%-75% and 0.2%-5.0%, respectively, indicated that DBDC was non-sensitizing. Four other sensitization studies (3 of which used the Magnusson-Kligman Maximization Method, the fourth used Guinea Pig Maximization at 0.5% for induction and 0.1% for challenge) were negative for sensitization. One test using the Freund's Complete Adjuvant method, with maximum test concentrations of 0.3% for pure DBDC and 3% of a 20% solution, found DBDC to possess distinct but weak sensitizing potential.

DBDC was non-phototoxic when tested on hairless mice at a concentrations up to 1% w/v in methanol or when tested on guinea pigs as a 20% solution in 2-phenoxyethanol. A photo-sensitization assay using guinea pigs and the 20% commercial formulation was also negative.

Subchronic Toxicity

Groups of four male and four female beagle dogs were exposed to 167, 1000, or 4000 ppm of DBDC (powder -98% active) in the feed for 13 weeks. The researchers

reported that dogs given the high dose had lesions of follicular cell hypertrophy and hyperplasia in the thyroid gland. The liver and spleen of the high dose dogs had pigment and increased extramedullary hematopoiesis. The researchers reported that no additional changes in the organs of any dosed group could be attributed solely to the administration of DBDC.

A follow up study further investigated the effects of DBDC on the thyroid gland. Four male and four female beagle dogs were fed a diet containing 167 ppm of DBDC for 13 weeks. At this dosage, there were no significant differences in levels of triiodothyronine or thyroxine (T_3 or T_4) between the dosed and control group of the same sex. At necropsy, treated dogs had an increased incidence of enlarged thyroid glands. The absolute and relative thyroid gland weights of dosed females were significantly higher than controls. Terminal body weight for both sexes and absolute and relative thyroid weights for males were comparable between dosed and control groups. The researchers were uncertain of the significance of the increased thyroid weight in treated females. Histopathologic findings were unremarkable.

Chronic Toxicity

No 2-year carcinogenicity studies of DBDC were identified in the available literature.

Short-Term Tests:

In Vitro

At concentrations up to 30 µg/plate, DBDC was negative in the Ames *Salmonella typhimurium* assay (strains not specified).

DBDC was also negative in the mouse lymphoma assay. L5178Y cells were incubated with DBDC at concentrations up to 7.1 µg/ml without S9 activation and up to 300 µg/ml with activation. While no raw data are presented, the researchers reported that the three highest dosed cultures without S9 activation had mutation frequencies of 3.8, 2.3, and 2.0 times greater than corresponding solvent controls. These values, however, were not considered statistically significant. Those incubated with S9 activation did not have any increase in mutation frequency compared to controls. Another mouse lymphoma assay found DBDC to be negative at concentrations of 2.1-28 µg/ml with S9 activation and 0.085-2.0 µg/ml without activation.

DBDC was not considered mutagenic in Chinese hamster V-79 cells at doses up to 50 µg/ml with S9 activation and up to 1 µg/ml without activation. It was reported that 0.3 µg/ml DBDC without S9 did exhibit a mutation frequency greater than 3 times that of negative controls (it was the lowest dose tested without activation). That 3-fold increase was not matched or surpassed by any other dose group with or without activation. DBDC was not considered mutagenic as the increase was neither statistically significant nor dose dependent.

When Chinese hamster ovary cells (CHO) were exposed to DBDC at concentrations of 6.20-11.03 µg/ml with S9 activation and 106.79-189.84 µg/ml without activation, significant dose dependent increases in the frequency of chromosome aberrations were noted in both study groups. In the high dose with S9 activation group, 28.0% of the cells had more than 1 aberration compared with 38.0% for the positive control and 4.0% for the solvent control. Without S9 activation, the highest dosed group had 34.0% cells with more than 1 aberration while the positive and solvent controls had 74.0% and 2.0%, respectively.

At concentrations up to 100 µg/ml with S9 activation and up to 10 µg/ml without S9 activation, DBDC did not induce unscheduled DNA synthesis in human IMR-90 fibroblasts.

No significant increase in transformation frequency was observed for BALB/3T3 mouse embryo cells exposed to DBDC for 3 days at a maximum concentration of 1.6 µg/ml without S9 activation, or exposed for 4 hours at a maximum concentration of 25 µg/ml with S9 activation. Survival rates for the highest dosed groups were 27% in the nonactivated study and 12% in the activated. In a similar study, BALB/C-3T3 cells were exposed to concentrations of DBDC between 17.6 to 82.5 µg/ml in the presence of S9 activation. Survival rates at the 82.5, 55.0 and 44.0 µg/ml dosage levels were 0, 4.1 and 80.2%, respectively. The transforming activity of cells treated with 55.0 µg/ml was twice that of the medium control; the value nearly attained statistical significance. However, as it was not part of an overall dose related response for the test material, DBDC was considered nontransforming.

In Vivo

DBDC did not induce dominant lethal mutations in male mice. Male mice (strain not specified) were maintained on diets containing 83.5, 500 and 3000 ppm DBDC for 8 weeks prior to mating and were then mated for 2 weeks with non-dosed females. The average pregnancy rate was 78% during week 1 and 60% for week 2. The researchers noted that there was no statistical difference in the incidence of any malformation observed between the negative control, the positive control, and the groups dosed with DBDC. That is, the mean incidence of resorption, fetal death, dead implants, and fetal viability as calculated on a per litter basis were comparable among all groups.

DBDC did not significantly increase chromosomal aberrations in rat bone marrow cells when five male and five female Sprague Dawley rats (weight not specified) were given a single administration by gavage of DBDC at a dosage of 100 mg/kg body weight. The animals were sacrificed at 8 and 12 hours post dosing and bone marrow cells arrested in metaphase were collected and analyzed. While no raw data are presented, the researchers reported that there was no significant increase in the percentage of chromosomal aberrations between control and dosed groups. In a similar study, male Sprague-Dawley rats were treated by gavage with either 5, 17, or 50 mg/kg/day of DBDC for 5 days. In a total of 750 bone marrow cells collected from the three groups combined 24 hours after the last dose, 4 chromosomal gaps were the only aberration noted. The value was not significant.

DBDC did not increase induction of aberrant wing spots in fruit flies. *Drosophila melanogaster* larvae were fed diets containing either 500 or 1000 ppm DBDC (99.85% pure) for 48 hours. The wing hairs were scored to measure mutagenic and recombinogenic activity. There was no difference in mutation rates between non-exposed controls and the dosed groups.

Metabolism: Following oral, dermal, or intravenous administration of ^{14}C-DBDC to rats, excretion via the urine accounted for recovery of > 50% of the applied radioactivity. Of tissues and body fluids, whole blood contained the highest levels of radioactivity. DBDC was readily absorbed by the dermal route.

Groups of 5 male and 5 female rats (strain and weight not specified) were given ^{14}C-DBDC as single oral doses of 5 mg/kg or 200 mg/kg, daily oral doses of 5 mg/kg for 15 days or a single intravenous dose of 5 mg/kg. Excretion via the urine accounted for recovery of > 64.6% of the radioactivity in all cases. At 168 hours post exposure and in all dosing groups, the whole blood contained the highest levels of radioactivity. When 3 male rats were tested following a single oral administration of 5 mg/kg, the peak mean blood level of radioactivity (4.34 µg equiv./g) was measured at 8 hours. At the Tissue Concentration max time determined to be 8 hours, the gastrointestinal tract and kidneys contained the highest levels of radioactivity. The concentration in other tissues was generally lower than in plasma with the exception of whole blood. At 48 hours, the highest mean levels of radioactivity were associated with whole blood.

Four hours after 5 mg/kg of ^{14}C-DBDC was dermally applied to rats (details not specified), a mean of 4.1% of the radioactivity was recovered in the excreta. It was estimated that 13% of the administered radioactivity had been absorbed by 4 hours. At 96 hours post dose, levels of radioactivity in tissues and fluids ranged from 0.02 to 0.62 µg equiv/g (representing 0.00-0.19% of the dose). At that time, a mean of 19.4% of the dose was recovered in urine, feces, and cage wash. It was estimated that approximately 22% of the administered radioactivity had been absorbed by 24 hours post dose.

Male Sprague Dawley rats (number not specified) were exposed to a 0.1 ml percutaneous dose of 1 mg/ml ^{14}C-DBDC. The researchers note that the purity of the dose solution,

88%, was low. At 72 hours approximately 40% of the applied radioactivity was recovered in the urine, feces, organs, and carcass. DBDC was concluded to be readily absorbed via the dermal route.

In vitro studies using excised skin from rats and humans established that DBDC was absorbed more readily when applied in aqueous solution than in sunscreen formulation. ^{14}C-DBDC (99% pure) in 250 µl of either water or sunscreen formulation was applied to the samples of excised skin. At 6 hours contact time, DBDC in the sunscreen formulation was absorbed by human skin to about 0.9%. It was estimated from steady-state absorption experiments that up to 2.3% and 5.3% of the applied DBDC in a sunscreen formulation could be absorbed following 12 and 24 hours of continuous contact time, respectively. DBDC in aqueous solution was more readily absorbed by both human and female rat skin, with approximately 33% being absorbed by human skin after 6 hours and 25% absorbed by female rat skin. Projections estimated that about 77.5% and 60.8% of the DBDC would be absorbed after 12 hours contact by human and female rat skin, respectively.

Other Biological Effects: No teratogenic effects were noted in the offspring of female rats (strain not specified) administered 25, 100, or 175 mg/kg DBDC by gavage on days 6 through 15 of gestation. No pharmacological signs of maternal toxicity were observed and there were no gross lesions observed at laparohysterectomy that were considered related to DBDC. Mean numbers of implantations, fetal weights, and the incidence of malformations and developmental variants were not significantly affected by DBDC. The average percent resorptions was significantly higher in the 175 mg/kg group (10.0%) than the control group (2.7%). However, 50% of the resorptions were clustered in two litters in the 175 mg/kg group. Because the incidence of resorptions in the 175 mg/kg group was within the normal range for historical controls, and other conventional signs of embryo-toxicity such as malformations and fetal weight reduction were not present, the increase in embryolethality was not considered biologically significant (Birnbaum *et al*., 1983).

A 90-day feeding study of rats exposed *in utero* and for 90 days after weaning to DBDC at doses up to 3000 ppm found no treatment related effects other than a slight increase in extramedullary hematopoiesis in the spleen of high dose females. Groups of 10 parental rats of each sex (strain not specified) were exposed to DBDC (83.5, 500 or 3,000 ppm) beginning 1 week prior to breeding and continuing throughout mating, gestation, and

lactation. For 90 days after weaning, 20 offspring/sex/dosing group were fed diets containing the same exposure levels on which their respective parents had been maintained. No treatment related clinical observations were noted in the parental generation. For the F_1 generation, male pups of the treated groups had body weights comparable to controls. High-dose female pups had lower body weights than controls, while low- and mid-dose female had higher body weights on two observation days. No treatment related ocular effects were noted.

Structure/Activity Relationships: Two structurally related chemicals were selected for evaluation of relative biological effects. No information on carcinogenicity or mutagenicity for the structurally related compounds 4-bromobutyronitrile [5332-06-9] or 6-bromohexanenitrile [6621-59-6] was found.

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